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EXAMINER

FALK, ANNE MARIE

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 11/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/478,099

Applicant(s)

ADAMIS ET AL.

Examiner

Anne-Marie Falk, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 January 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☒ Interview Summary (PTO-413)
Paper No(s)/Mail Date 6/29/04
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

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DETAILED ACTION

The amendment filed August 13, 2004 (herein after referred to as "the response") has been entered. No claims have been amended. Claim 21 has been cancelled.

Accordingly, Claims 1-18 are pending in the instant application.

The rejection of Claim 21 under 35 U.S.C. 112, first paragraph, for including new matter, is withdrawn in view of the cancellation of this claim. The arguments presented at pages 4-5 of the response have been fully considered but are rendered moot by cancellation of the claim.

Applicants' Request for Telephonic Interview

At page 1 of the response Applicants request a telephonic interview. A telephonic interview after final rejection was granted on June 29, 2004. A second interview after final rejection is not proper and will not be granted. Applicants are further advised that all interview requests should be submitted directly to the Examiner using the Interview Request Form PTOL-413A. See MPEP § 713.01.

Information Disclosure Statement

While it is noted that Applicants' RCE Transmittal form dated August 13, 2004 states that an Information Disclosure Statement, PTO-1449, and copies of cited references were submitted, the Examiner has not received any of these items. Applicant is advised to resubmit the documents for consideration.

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Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 13, 2004 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims include new matter.

In the amendment of 11/20/02, Claim 1 was amended to add the limitation "a scleral surface of the eye with a nucleic acid molecule having a molecular weight no greater than 150 kDa such that the nucleic acid passes through the sclera and into the interior of the eye." In the amendment of 9/22/03, Claim 5 was amended to add the limitation "and a molecular weight no greater than 150 kDa." However, the as-filed specification does not provide specific support for a nucleic acid molecule having a molecular weight no greater than 150 kDa. In the amendment of 11/20/02, as support for the amendment to Claim 1, Applicants point to the specification at page 13, lines 8 and 16-18 and Example 1. However, page 13,

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line 8 only refers to nucleic acid molecules broadly, but does not refer to a molecular weight limitation.

At lines 16-18 of page 13, the specification merely states:

“The invention also feature method of delivery a therapeutic or diagnostic agent to the eye of a mammal, where the agent is delivered through sclera which has been treated to thin it, for example, by surgical means.”

Again, the cited passage does not refer to a molecular weight limitation for the nucleic acid molecule.

Example 1 of the specification, also cited as support for the amendment to Claim 1, describes an experiment that measures the permeability of dissected sclera to a variety of compounds having varied molecular weights. Table 1 summarizes the results obtained. However, none of the compounds tested were nucleic acid molecules and the cited section does not refer to a nucleic acid molecule “having a molecular weight no greater than 150 kDa.” Thus, the cited sections do not provide support for the amendment to the claims.

Therefore, the amended claims include new matter.

Enablement

Claims 1-15 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering a nucleic acid having a molecular weight no greater than 50 kDa into the interior of the eye via passage through the sclera, does not reasonably provide enablement for transcleral delivery of nucleic acids larger than 50 kDa. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant is advised that the specification does not provide specific support for claim language such as “no greater than 50 kDa.” Thus, although a scope of enablement is indicated, Applicants should not assume that the Examiner is suggesting specific claim language. It is up to Applicant to come up with

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claim language (e.g., specific disclosed embodiments) directed to subject matter that falls within the indicated scope of enablement.

At page 6, paragraph 2 of the response, Applicants submit that the specification complies with the requirements of 35 U.S.C. 112, first paragraph because it provides a description for applying a nucleic acid molecule to the outer surface of the eye for transfer through the sclera and to methods for actually detecting transfer of molecules of interest through the sclera. Applicants go on to argue that the skilled artisan could use the *in vitro* diffusion apparatus and the protocol described in Example 1 to determine whether a nucleic acid having a molecular weight no greater than 150 kDa can pass through scleral tissue. However, the claims are not directed to a method of **detecting** transfer of nucleic acid molecules through the sclera, but rather are directed to **actually achieving transfer** of nucleic acid molecules as large as 150 kDa. Contrary to Applicants' arguments, the specification does not teach that contact with the sclera is sufficient to permit the transfer of nucleic acid molecules as large as 150 kDa into the interior of the eye, particularly in amounts that would be therapeutic, given the unpredictability in the gene delivery art and the limited teachings of the specification. It is not sufficient to provide a method for detecting nucleic acid transfer when the claims are directed to actually achieving nucleic acid transfer. When the claims are directed to nucleic acid delivery, the specification must provide sufficient guidance for actually achieving nucleic acid delivery for the full scope of the claim. In this case, the claims cover delivery of nucleic acid molecules as large as 150 kDa, but the specification does not teach how to achieve delivery of nucleic acid molecules larger than 50 kDa. Applicants are reminded that the specification does not assert a utility for transferring nucleic acid molecules non-therapeutically. Thus, the specification must teach how to use the claimed method to deliver nucleic acid molecules to the interior of the eye in amounts that would be sufficient to achieve a therapeutic effect, in a location where the nucleic acid molecules could actually have a therapeutic effect.

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At page 6, paragraph 4 of the response, Applicants refer to the Declaration of Dr. Carrasquillo and assert that the declaration describes an *in vivo* experiment that demonstrates that an anti-VEGF aptamer, can traverse the sclera and exert a biological effect within the interior of the eye. However, the experiments described in the Declaration do not provide evidence of enablement for nucleic acids larger than 50 kDa, which is the maximum molecular weight of a nucleic acid delivered transclerally in the experiments described therein. Thus, Applicants' arguments are not commensurate in scope with the scope of the claims.

At page 7, paragraph 1 of the response, Applicants argue that the claims are not necessarily directed to methods of gene therapy because all that is required is that a particular nucleic acid traverse the sclera and enter the interior of the eye. This argument has already been addressed in the Office Action mailed 2/13/04 at pages 4-5. It is well established in our law that the specification must teach how to use the claimed invention. The only asserted utility for delivering nucleic acid molecules to the interior of the eye is for therapy (see specification at page 8, lines 18-19; page 9, lines 5-15; and page 13, lines 8-10). Thus, the claims are clearly directed to methods of gene therapy. Contrary to Applicants' argument, Claims 16 and 17 explicitly require that the method provide a therapeutic effect for a variety of retinal or choroidal diseases. Thus, Applicants' arguments are not commensurate in scope with the scope of the claims.

At page 7, paragraph 2 of the response, Applicants reiterate their argument from page 6, paragraph 2. This argument has already been addressed herein above.

At page 7, paragraphs 3-4 and page 8, paragraphs 1-2 of the response, Applicants argue that a "means for facilitating transport of the nucleic acid across the sclera" is not required and that encapsulation into PLGA microspheres is also not required for delivery of the nucleic acid to the interior of the eye. The Declaration of Dr. Carrasquillo also states that she does not believe that encapsulation was necessary to facilitate delivery of the nucleic acid through the sclera. In view of the Declaration and

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arguments, the Examiner accepts that a “means for facilitating transport of the nucleic acid across the sclera” is not required and the indicated scope of enablement is commensurate with this understanding of the claimed invention.

At page 8, paragraph 4 of the response, Applicants assert that the claimed delivery method has general applicability and need not be limited to a particular nucleic acid molecule. In view of the indicated scope of enablement, this argument is moot with respect to Claims 1-15 and 18. Insofar as this argument is applied to Claims 16 and 17, the Examiner strongly disagrees. Claims 16 and 17 are explicitly directed to a method that provides a therapeutic effect for a variety of retinal or choroidal diseases. Absent a teaching of nucleic acids appropriate for treating the broad scope of retinal and choroidal diseases covered by the claims, the skilled artisan would not be able to practice the claimed invention without undue experimentation, for reasons of record.

Claims 16 and 17 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

For the reasons discussed above and in the previous Office Actions, the specification fails to provide an enabling disclosure for treating a retinal or choroidal disease. Thus, there is no scope of enablement for the treatment claims

Written Description

Claims 1-18 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 8-10 of the Office Action of Paper No. 13 (mailed 5/21/02), pages 4-5 of the Office Action of Paper No. 22 (mailed 6/3/03), pages 6-8 of the Office Action mailed 2/13/04, and for the reasons

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discussed herein below, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

The specification still must describe nucleic acid molecules that are suitable for use in the claimed method. That is, nucleic acids that have a molecular weight no greater than 50 kDa and which are useful therapeutically or diagnostically.

At page 9 of the response, Applicants assert that the claimed delivery method is one of general applicability and thus should not be limited to any particular nucleic acid molecule. However, Applicants are reminded that the claims encompass treatment methods that do require specific nucleic acid molecules that are appropriate for treatment for specific diseases. Claims 16 and 17 are exclusively directed to treatment methods. Applicants are further reminded of the court decision of *In re Shokal*, 113 USPQ 283 (CCPA 1957) which states that

"It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189 ; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary."

Thus, when the claims are generic with regard to the nucleic acid, the written description requirement calls for the specification to describe a sufficient variety of nucleic acid molecules that are

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suitable for use in the claimed method, such that the described nucleic acids support the full scope of the claims. That is, nucleic acids that have a molecular weight no greater than 50 kDa and which are useful therapeutically or diagnostically. In such a situation, where the written description supports genus claims, the claims would not be limited to a "particular nucleic acid molecule" as Applicants argue. However, since the instant specification does not describe a sufficient variety of nucleic acid molecules that are suitable for use in the claimed method, it does not support genus claims. Furthermore, since the instant specification does not describe a single species of nucleic acid molecule suitable for use in the claimed method, it does not support species claims.

Applicants are again reminded that Claims 16 and 17 are explicitly and exclusively directed to treatment of retinal and choroidal disease. Thus, the specification must describe nucleic acid molecules that could be used to treat a variety of retinal and choroidal diseases, using the claimed delivery method. The specification does not describe a single nucleic acid that could be used according to the claimed method to treat macular degeneration, diabetic retinopathy, retinitis pigmentosa and other retinal degenerations, retinal vein occlusions, sickle cell retinopathy, glaucoma, choroidal neovascularization, retinal neovascularization, retinal edema, retinal ischemia, proliferative vitreoretinopathy, or retinopathy of prematurity, as claimed. In the absence of a written description of the nucleic acid agent, the claimed method lacks written description because the nucleic acid agent is an essential element of the claimed method.

At page 10, paragraph 2 of the response, Applicants assert that, to the extent the claims relate to delivery of nucleic acids useful in treating certain ocular disorders, suitable nucleic acid sequences were available in the art and would have been known to the skilled artisan. As evidence, Applicants point to their "previous Amendment and Response" where Applicants claim that they have made of record a variety of documents that describe a variety of nucleic acids that had been delivered to the eye by other routes, such as by intravitreal injection, prior to the filing date of this application. Applicants assert that

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this invention provides another route to get such nucleic acids into the eye. Contrary to Applicants arguments, the references to which Applicants refer do not teach nucleic acids that could be delivered in accordance with the claimed method because the nucleic acids of the references are not 50 kDa or smaller. For example, one of the references cited, WO 97/15330, describes the intravitreal injection of a fluorescein-labelled oligonucleotide designated CATSCF in Example 2, but the reference does not indicate that the molecule is smaller than 50 kDa in size nor that it is suitable for treating the wide variety of retinal and choroidal diseases covered by the claims. Therefore, the agent would not be suitable for delivery by the claimed method. Furthermore, while the reference states that the oligonucleotide is directed against human cathepsin S, it does not actually **describe** the oligonucleotide. Thus, Applicants arguments are not commensurate in scope with the scope of the claimed invention.

Conclusion

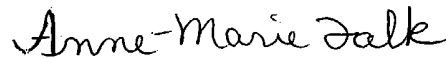
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.



ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER